REMARKS

Claims 1 and 70 to 75 were pending prior to this response. By the present communication, the paragraph of the specification beginning at line 3 of page 18 has been amended to correct inadvertent omission of the term "of". No claims have been added or cancelled or amended by the present communication. According, claims 1 and 70-75 are currently pending.

The Rejection under 35 U.S.C. § 112, first paragraph

Applicants respectfully traverse the rejection of claims 1 and 70-75 under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient description in the Specification so that those of skill in the art could make and use the invention without undue experimentation. Although the Office Action states that claims 1 and 70-75 are rejected, the statement is also made that the rejection has been extended to new claims 70-75. Therefore, the following remarks are made on the assumption that the Examiner intended the rejection to pertain to claims 1 and 70-75. If this assumption is incorrect, Applicant requests the Examiner to call the undersigned to discuss the rejection.

The invention methods for inhibiting production of the Aβ11-40/42 peptide fragments, as defined by claim 1, require "contacting a sample or cell containing a beta-site APP-cleaving enzyme 1 (BACE1) and an amyloid precursor protein (APP) *in vitro* with an antibody specific for BACE1, whereby the antibody inhibits BACE1 cleavage of APP, thereby inhibiting the production of Aβ11-40/42 peptide fragments."

The Examiner cites Yan et al. (*The Journal of Biological Chemistry* 276(39):36788-36796 (2001), as showing the difficulty of producing anti-BACE1 antibodies that disrupt BACE1 activity. However, the antibodies disclosed in Yan et al. target an antigen between

amino acids 191 and 501 of the APP protein. In keeping with the focus of the Yan et al. studies, these regions of the protein are related to the transmembrane domain of the APP protein. As shown by Fig. 1 of R.Vassar (*Journal of Molecular Neuroscience* 17(2):157-170, 2001; of record herein), the cleavage site of the secretase does not lie within the transmembrane region. Of more importance, the antibodies discussed by Yan et al. are not anti-BACE1 antibodies at all.

The Examiner further asserts that Vassar illustrates the difficulty of obtaining inhibitors of BACE1, allegedly showing that undue experimentation would be required to produce antibody for use in the invention methods, as recited in claim 1. However, Vassar is not concerned with development of antibodies. Instead, Vassar is concerned with development of small molecule inhibitors of BACE1, especially small molecule inhibitors that will cross the blood brain barrier, requirements that do not pertain to Applicants' claimed *in vitro* methods for inhibiting production of Aβ11-40/42 peptides in a sample or cell. Applicant's claims to not recite small molecule inhibitors and do not recite use of anti-BACE1 antibodies in a treatment modality.

Both Yan et al. and Vassar are silent regarding any difficulty in producing anti-BACE1 *antibodies* that inhibit production of Aβ11-40/42 peptide fragments from APP cleavage *in vitro*. Thus, Applicant submits that the comments of Yan et al. and Vassar regarding anti-APP antibodies and small molecule inhibitors of BACE1 are not dispositive on the issue of enablement of the subject matter of Applicants' claims.

However, M. Farzan et al. (of record herein) disclose that an Arg-296 → Lys mutation of BACE1 interferes with the ability of the enzyme to cleave at the β site of APP. M. Farzan et al. also disclose that BACE1 cleaves Aβ after Tyr-10 (See Fig 3 of Farzan) and, based on this information, opines: "Peptide variants based on the sequence of this site could presumably serve as models for small molecules that specifically inhibit BACE1" (Farzan et al, page 9717, col 2).

Vassar at al. also show that information concerning the BACE1 active site was known in the art at the filing of the present application. Vassar et al. refer to earlier studies that produced models of the BACE1 active site. The first is a molecular modeling study of BACE1 active site bound with wild type and mutant APP proteins (J.M. Sauder et al, *J. Mol. Biol.* 300:241-248,

2000) *and* the second is an X-ray structure of the BACE1 protease domain as co-crystallized with a transition-state inhibitor (L. Hong et al. *Science* 290:150-153, 2000) (Cited in Vassar, page 167, Col 1) (Applicants refer to the latter study in the specification, page 58, lines 26-28). Both of these studies provide information about the active site of the enzyme to which the invention antibodies bind and both studies were known in the art at the filing of this application.

Taken together, such studies show that much was known about the location and shape of the active site of the BACE1 molecule at the filing of the present application. Further, those of skill in the art would understand that an antibody that would bind to the active site of the enzyme would inhibit its enzymatic activity and hence "inhibit production of Aβ11-40/42 peptide fragments", the cleavage products formed by activity of BACE1.

Applicants respectfully submit that those of skill in the art would understand how to use a peptide, e.g., of 8-12 amino acids in length, based on the BACE1 cleavage site in APP and the structural models of BACE1 to obtain antibodies that could be screened for binding to the active site of BACE1 enzyme. The screening of antibodies for specificity and avidity is considered routine experimentation in the art.

Applicants respectfully submit that the technical procedures for developing antibodies that bind to and, hence, inactivate the active site of an enzyme can be practiced without undue experimentation by those of skill in the art without undue experimentation. Therefore, based on the skill of the art and the teaching in the Specification, those of skill in the art could obtain an anti-BACE1 antibody that would disrupt BACE1 activity. Accordingly, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions related to this matter.

Respectfully submitted,

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